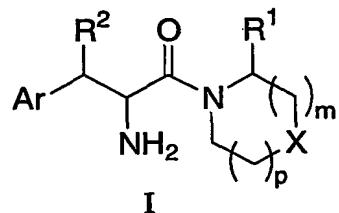


WHAT IS CLAIMED IS:

1. A compound of structural formula I:



5 or a pharmaceutically acceptable salt thereof; wherein
each n is independently 0, 1, or 2;
m and p are independently 0 or 1;
q is 1 or 2;

10 X is CH₂, S, CHF, or CF₂;

Ar is phenyl, unsubstituted or substituted with one to five R³ substituents;

R¹ is hydrogen or cyano;

15 R² is selected from the group consisting of
C₁-10 alkyl, wherein alkyl is unsubstituted or substituted with one to five substituents
independently selected from halogen or hydroxy,
C₂-10 alkenyl, wherein alkenyl is unsubstituted or substituted with one to five
20 substituents independently selected from halogen or hydroxy,
(CH₂)_n-aryl, wherein aryl is unsubstituted or substituted with one to five substituents
independently selected hydroxy, halogen, CO₂H, C₁-6 alkyloxycarbonyl, C₁-6
alkyl, and C₁-6 alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted
with one to five halogens,
25 (CH₂)_n-heteroaryl, wherein heteroaryl is unsubstituted or substituted with one to three
substituents independently selected from hydroxy, halogen, CO₂H, C₁-6
alkyloxycarbonyl, C₁-6 alkyl, and C₁-6 alkoxy, wherein alkyl and alkoxy are
unsubstituted or substituted with one to five halogens,

(CH₂)_n-heterocyclyl, wherein heterocyclyl is unsubstituted or substituted with one to three substituents independently selected from oxo, hydroxy, halogen, CO₂H, C₁-6 alkyloxycarbonyl, C₁-6 alkyl, and C₁-6 alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens,

5 (CH₂)_n-C₃-6 cycloalkyl, wherein cycloalkyl is unsubstituted or substituted with one to three substituents independently selected from halogen, hydroxy, CO₂H, C₁-6 alkyloxycarbonyl, C₁-6 alkyl, and C₁-6 alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens,

10 (CH₂)_nCOOH,

(CH₂)_nCOOC₁-6 alkyl,

(CH₂)_nCONR⁴R⁵, wherein R⁴ and R⁵ are independently selected from the group consisting of hydrogen, tetrazolyl, thiazolyl, (CH₂)_n-phenyl, (CH₂)_n-C₃-6 cycloalkyl, and C₁-6 alkyl, wherein alkyl is unsubstituted or substituted with one to five halogens and wherein phenyl and cycloalkyl are unsubstituted or

15 substituted with one to five substituents independently selected from halogen, hydroxy, C₁-6 alkyl, and C₁-6 alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens;

or R⁴ and R⁵ together with the nitrogen atom to which they are attached form a heterocyclic ring selected from azetidine, pyrrolidine, piperidine, piperazine, and morpholine wherein said heterocyclic ring is unsubstituted or substituted with one to five substituents independently selected from halogen, hydroxy, C₁-6 alkyl, and C₁-6 alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens; and

20 wherein any methylene (CH₂) carbon atom in R² is unsubstituted or substituted with one to two groups independently selected from halogen, hydroxy, C₁-4 alkyl, and C₁-4 alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens;

25 each R³ is independently selected from the group consisting of

30 halogen,

cyanato,

hydroxy,

C₁-6 alkyl, wherein alkyl is unsubstituted or substituted with one to five halogens,

C₁-6 alkoxy, wherein alkoxy is unsubstituted or substituted with one to five halogens,

phenyloxy, unsubstituted or substituted with one to five substituents independently selected from halogen, hydroxy, CO₂H, cyano, C₁-6 alkyloxycarbonyl, C₁-6 alkyl, and C₁-6 alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens;

5 (CH₂)_n-NR⁴R⁵,

(CH₂)_n-CONR⁴R⁵,

(CH₂)_n-OCONR⁴R⁵,

(CH₂)_n-SO₂NR⁴R⁵,

(CH₂)_n-SO₂R⁶,

10 (CH₂)_n-NR⁷SO₂R⁶,

(CH₂)_n-NR⁷CONR⁴R⁵,

(CH₂)_n-NR⁷COR⁷,

(CH₂)_n-NR⁷CO₂R⁶,

(CH₂)_n-COOH,

15 (CH₂)_n-COOC₁-₆ alkyl,

(CH₂)_q-aryl, wherein aryl is unsubstituted or substituted with one to five substituents independently selected from halogen, hydroxy, CO₂H,

C₁-6 alkyloxycarbonyl, C₁-6 alkyl, C₃-6 cycloalkyl, and C₁-6 alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens,

20 (CH₂)_q-heteroaryl, wherein heteroaryl is unsubstituted or substituted with one to three substituents independently selected from hydroxy, halogen, CO₂H, C₁-6 alkyloxycarbonyl, C₁-6 alkyl, C₃-6 cycloalkyl, and C₁-6 alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens,

25 (CH₂)_q-heterocyclyl, wherein heterocyclyl is unsubstituted or substituted with one to three substituents independently selected from oxo, hydroxy, halogen, CO₂H, C₁-6 alkyloxycarbonyl, C₁-6 alkyl, C₃-6 cycloalkyl, and C₁-6 alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens,

30 (CH₂)_n-C₃-₆ cycloalkyl, wherein cycloalkyl is unsubstituted or substituted with one to three substituents independently selected from halogen, hydroxy, C₁-6 alkyl, and C₁-6 alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens,

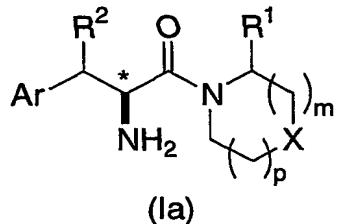
wherein any methylene (CH₂) carbon atom in R³ is unsubstituted or substituted with one to two groups independently selected from halogen, hydroxy, C₁-4 alkyl, and C₁-4

alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens;

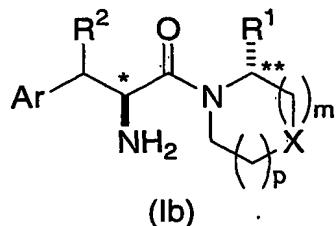
5 R⁶ is independently selected from the group consisting of tetrazolyl, thiazolyl, (CH₂)_n-phenyl, (CH₂)_n-C₃-6 cycloalkyl, and C₁-6 alkyl, wherein alkyl is unsubstituted or substituted with one to five halogens and wherein phenyl and cycloalkyl are unsubstituted or substituted with one to five substituents independently selected from halogen, hydroxy, C₁-6 alkyl, and C₁-6 alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens, and wherein any methylene (CH₂) carbon atom in R⁶ is unsubstituted or substituted with one to two groups
10 independently selected from halogen, hydroxy, and C₁-4 alkyl unsubstituted or substituted with one to five halogens; and

each R⁷ is hydrogen or R⁶.

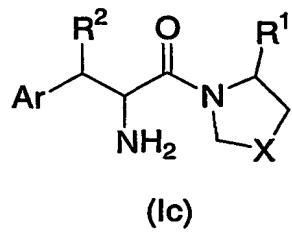
15 2. The compound of Claim 1 wherein the carbon atom marked with an * has the stereochemical configuration as depicted in formula Ia:



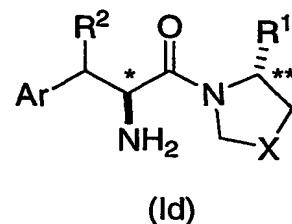
3. The compound of Claim 2 wherein the carbon atom attached to R¹ marked with an ** has the stereochemical configuration as depicted in formula Ib:



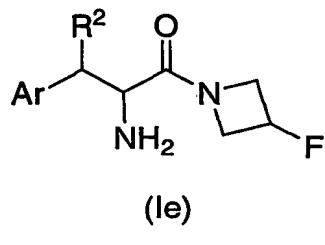
4. The compound of Claim 1 of the structural formula Ic:



5. The compound of Claim 4 wherein the carbon atom marked with an * and
5 the carbon atom marked with an ** have the stereochemical configurations as depicted in
formula Id:

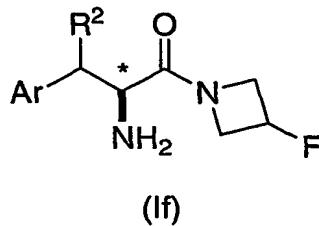


6. The compound of Claim 1 of the structural formula Ie

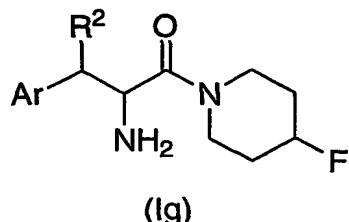


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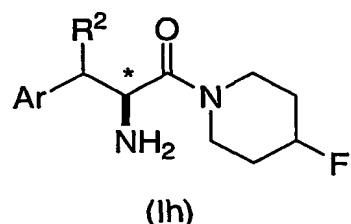
7. The compound of Claim 6 wherein the carbon atom marked with an * has
the stereochemical configuration as depicted in formula If:



8. The compound of Claim 1 of the structural formula Ig



9. The compound of Claim 8 wherein the carbon atom marked with an * has the stereochemical configuration as depicted in formula Ih:



5

10. The compound of Claim 1 wherein R² is selected from the group consisting of

C₁₋₆ alkyl, wherein alkyl is unsubstituted or substituted with one to five substituents independently selected from halogen or hydroxy,

10 C₂₋₆ alkenyl, wherein alkenyl is unsubstituted or substituted with one to five substituents

independently selected from halogen or hydroxy,

(CH₂)_n-C₃₋₆ cycloalkyl, wherein cycloalkyl is unsubstituted or substituted with one to three substituents independently selected from halogen, hydroxy, CO₂H, C₁₋₆ alkyloxycarbonyl, C₁₋₆ alkyl, and C₁₋₆ alkoxy, wherein alkyl and alkoxy are

15 unsubstituted or substituted with one to five halogens,

(CH₂)_nCOOH,

(CH₂)_nCOOC₁₋₆ alkyl, and

17 (CH₂)_nCONR⁴R⁵, wherein R⁴ and R⁵ are independently selected from the group consisting of hydrogen, tetrazolyl, thiazolyl, (CH₂)_n-phenyl, (CH₂)_n-C₃₋₆

cycloalkyl, and C₁₋₆ alkyl, wherein alkyl is unsubstituted or substituted with one to five halogens and wherein phenyl and cycloalkyl are unsubstituted or substituted with one to five substituents independently selected from halogen, hydroxy, C₁₋₆ alkyl, and C₁₋₆ alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens;

5 or R⁴ and R⁵ together with the nitrogen atom to which they are attached form a heterocyclic ring selected from pyrrolidine, piperidine, piperazine, and morpholine wherein said heterocyclic ring is unsubstituted or substituted with one to five substituents independently selected from halogen, hydroxy, C₁₋₆ alkyl, and C₁₋₆ alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens; and

10 wherein any methylene (CH₂) carbon atom in R² is unsubstituted or substituted with one to two groups independently selected from halogen, hydroxy, C₁₋₄ alkyl, and C₁₋₄ alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens.

15 11. The compound of Claim 10 wherein R² is selected from the group consisting of

15 C₁₋₃ alkyl, wherein alkyl is unsubstituted or substituted with one to five substituents independently selected from halogen or hydroxy,

20 CH₂-C₃₋₆ cycloalkyl,

COOH,

COOC₁₋₆ alkyl, and

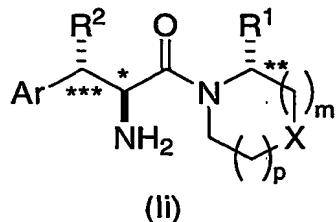
25 CONR⁴R⁵, wherein R⁴ and R⁵ are independently selected from the group consisting of hydrogen, tetrazolyl, thiazolyl, (CH₂)_n-phenyl, (CH₂)_n-C₃₋₆ cycloalkyl, and C₁₋₆ alkyl, wherein alkyl is unsubstituted or substituted with one to five halogens and wherein phenyl and cycloalkyl are unsubstituted or substituted with one to five substituents independently selected from halogen, hydroxy, C₁₋₆ alkyl, and C₁₋₆ alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens;

30 or R⁴ and R⁵ together with the nitrogen atom to which they are attached form a heterocyclic ring selected from pyrrolidine, piperidine, piperazine, and morpholine wherein said heterocyclic ring is unsubstituted or substituted with one to five substituents independently selected from halogen, hydroxy, C₁₋₆ alkyl, and C₁₋₆ alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens.

35 12. The compound of Claim 11 wherein R² is selected from the group consisting of
methyl,
ethyl,

5 CH₂-cyclopropyl,
 COOH,
 COOMe,
 COOEt,
 CONMe₂,
 CONH₂,
 CONHMe,
 CONHEt,
 pyrrolidin-1-ylcarbonyl,
 10 azetidin-1-ylcarbonyl, and
 [(tetrazol-5-yl)amino]carbonyl.

13. The compound of Claim 1 wherein the carbon atom marked with an *, the carbon atom attached to R¹ marked with an **, and the carbon atom attached to R² marked with 15 an *** have the stereochemical configurations as depicted in formula II:



R² is selected from the group consisting of

C₁₋₆ alkyl, wherein alkyl is unsubstituted or substituted with one to five substituents

independently selected from halogen or hydroxy,

20 (CH₂)_n-C₃₋₆ cycloalkyl,

COOH,

COOC₁₋₆alkyl, and

CONR⁴R⁵, wherein R⁴ and R⁵ are independently selected from the group consisting of hydrogen, tetrazolyl, thiazolyl, (CH₂)_n-phenyl, (CH₂)_n-C₃₋₆ cycloalkyl, and C₁₋₆

25 alkyl, wherein alkyl is unsubstituted or substituted with one to five halogens and wherein phenyl and cycloalkyl are unsubstituted or substituted with one to five substituents independently selected from halogen, hydroxy, C₁₋₆ alkyl, and C₁₋₆ alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens;

or wherein R⁴ and R⁵ together with the nitrogen atom to which they are attached form a heterocyclic ring selected from pyrrolidine, piperidine, piperazine, and morpholine wherein said heterocyclic ring is unsubstituted or substituted with one to five substituents independently selected from halogen, hydroxy, C₁₋₆ alkyl, and C₁₋₆ alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens; and

each R³ is independently selected from the group consisting of:

halogen,

hydroxy,

C₁₋₆ alkyl, wherein alkyl is unsubstituted or substituted with one to five halogens,

C₁₋₆ alkoxy, wherein alkoxy is unsubstituted or substituted with one to five halogens, phenoxy, unsubstituted or substituted with one to three substituents independently selected from halogen, hydroxy, cyano, C₁₋₆ alkyl, and C₁₋₆ alkoxy, wherein

alkyl and alkoxy are unsubstituted or substituted with one to five halogens; and (CH₂)_n-C₃₋₆ cycloalkyl, wherein cycloalkyl is unsubstituted or substituted with one to three substituents independently selected from halogen, hydroxy, C₁₋₆ alkyl, and C₁₋₆ alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens.

20

14. The compound of Claim 13 wherein R² is selected from the group consisting of

methyl,

ethyl,

25 CH₂-cyclopropyl,

COOH,

COOMe,

COOEt,

CONMe₂,

30 CONH₂,

CONHMe,

CONH₂Et,

pyrrolidin-1-ylcarbonyl,

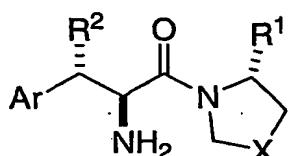
azetidin-1-ylcarbonyl, and

[(tetrazol-5-yl)amino]carbonyl.

15. The compound of Claim 14 wherein R³ is selected from the group consisting of:

- 5 fluoro,
- chloro,
- bromo,
- trifluoromethyl,
- trifluoromethoxy, and
- 10 methoxy.

16. The compound of Claim 1 of the structural formula Ij



(Ij)

wherein X is CH₂, S, CHF, or CF₂;

- 15 Ar is phenyl, unsubstituted or substituted with one to five R³ substituents;
- R¹ is hydrogen or cyano;

R² is selected from the group consisting of

C₁₋₆ alkyl, wherein alkyl is unsubstituted or substituted with one to five substituents

- 20 independently selected from halogen or hydroxy,
- (CH₂)_n-C₃₋₆ cycloalkyl,
- COOH,
- COOC₁₋₆ alkyl, and

- 25 CONR⁴R⁵, wherein R⁴ and R⁵ are independently selected from the group consisting of hydrogen, tetrazolyl, thiazolyl, (CH₂)_n-phenyl, (CH₂)_n-C₃₋₆ cycloalkyl, and C₁₋₆ alkyl, wherein alkyl is unsubstituted or substituted with one to five halogens and wherein phenyl and cycloalkyl are unsubstituted or substituted with one to five substituents independently selected from halogen, hydroxy, C₁₋₆ alkyl, and C₁₋₆

alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens;

or R⁴ and R⁵ together with the nitrogen atom to which they are attached form a heterocyclic ring selected from pyrrolidine, piperidine, piperazine, and morpholine wherein said heterocyclic ring is unsubstituted or substituted with one to five substituents independently selected from halogen, hydroxy, C₁₋₆ alkyl, and C₁₋₆ alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens; and

10 each R³ is independently selected from the group consisting of:

halogen,

C₁₋₆ alkyl, wherein alkyl is unsubstituted or substituted with one to five halogens,

C₁₋₆ alkoxy, wherein alkoxy is unsubstituted or substituted with one to five halogens,

15 phenoxy, unsubstituted or substituted with one to three substituents

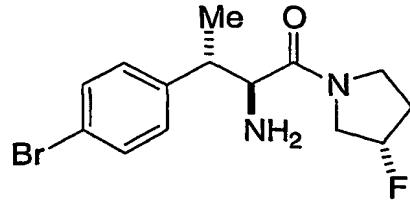
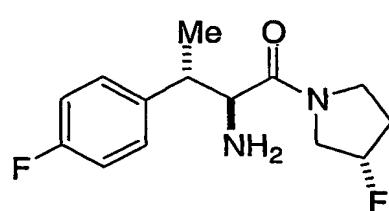
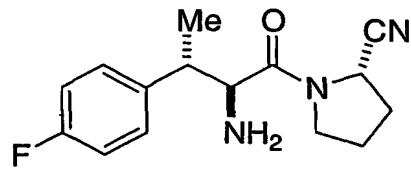
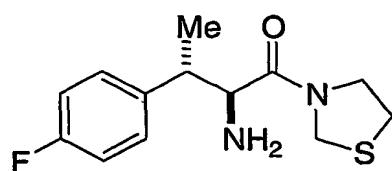
independently selected from halogen and cyano, and

phenyl(CH₂)_nCON(Me)-, wherein phenyl is unsubstituted or

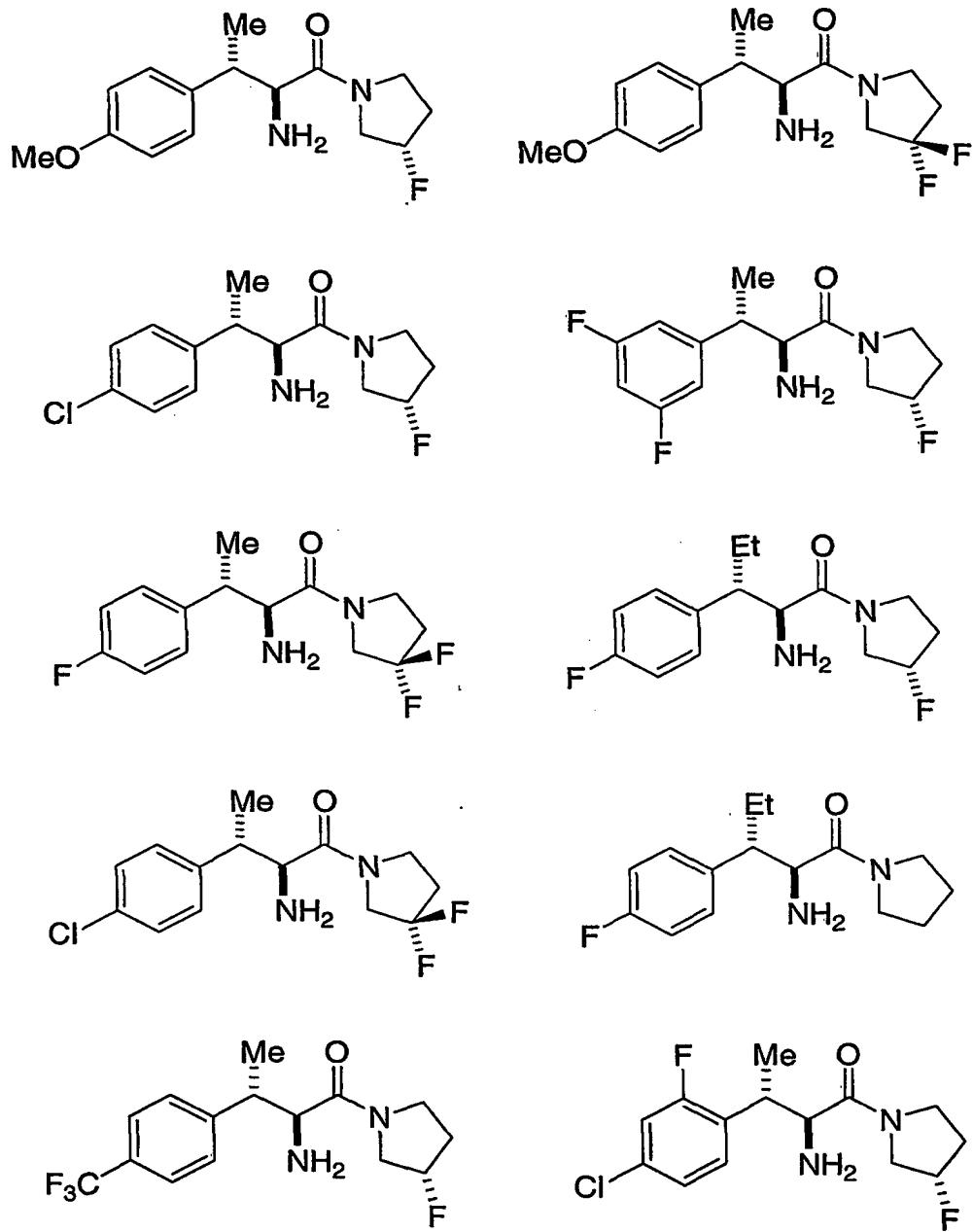
substituted with one to three substituents independently selected from halogen, trifluoromethyl, and C₁₋₄ alkyl.

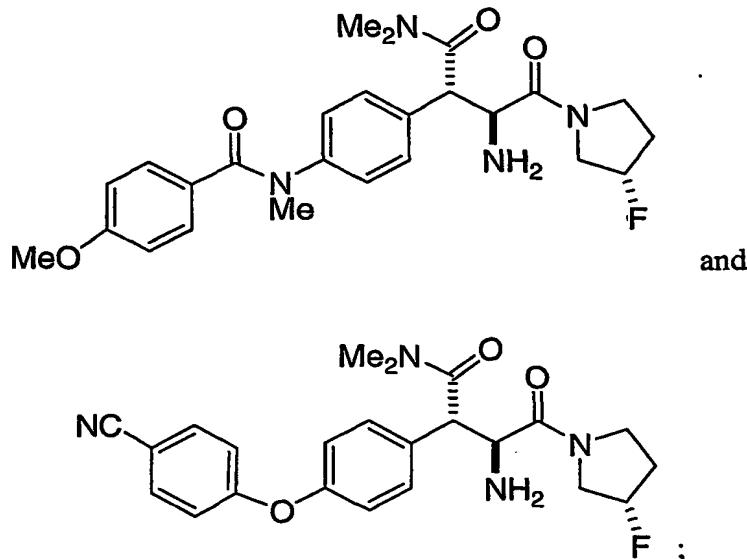
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17. The compound of Claim 16 of the structural formula selected from the group consisting of



25





or a pharmaceutically acceptable salt thereof.

5 18. A pharmaceutical composition which comprises a compound of Claim 1
and a pharmaceutically acceptable carrier.

10 19. A method for inhibiting dipeptidyl peptidase-IV enzyme activity in a
mammal in need thereof which comprises the administration to the mammal of an effective
amount of a compound of Claim 1.

15 20. A method for treating diabetes in a mammal in need thereof which
comprises the administration to the mammal of a therapeutically effective amount of a compound
of Claim 1.

21. A method for treating non-insulin dependent (Type 2) diabetes in a
mammal in need thereof which comprises the administration to the mammal of a therapeutically
effective amount of a compound of Claim 1.

20 22. A method for treating hyperglycemia in a mammal in need thereof which
comprises the administration to the mammal of a therapeutically effective amount of a compound
of Claim 1.

23. A method for treating obesity in a mammal in need thereof which comprises the administration to the mammal of a therapeutically effective amount of a compound of Claim 1.

5 24. A method for treating one or more lipid disorders selected from the group of dyslipidemia, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, low HDL and high LDL in a mammal in need thereof which comprises the administration to the mammal of a therapeutically effective amount of a compound of Claim 1.

10 25. A method for treating in a mammal in need thereof one or more conditions selected from the group consisting of (1) hyperglycemia, (2) low glucose tolerance, (3) insulin resistance, (4) obesity, (5) lipid disorders, (6) dyslipidemia, (7) hyperlipidemia, (8) hypertriglyceridemia, (9) hypercholesterolemia, (10) low HDL levels, (11) high LDL levels, (12) atherosclerosis and its sequelae, (13) vascular restenosis, (14) irritable bowel syndrome, (15) inflammatory bowel disease, including Crohn's disease and ulcerative colitis, (16) other inflammatory conditions, (17) pancreatitis, (18) abdominal obesity, (19) neurodegenerative disease, (20) retinopathy, (21) nephropathy, (22) neuropathy, (23) Syndrome X, (24) ovarian hyperandrogenism (polycystic ovarian syndrome), and other disorders where insulin resistance is a component, wherein the method comprises the administration to the mammal a therapeutically effective amount of a compound of Claim 1.

26. The pharmaceutical composition of Claim 18 further comprising one or more additional active ingredients selected from the group consisting of:

(a) a second dipeptidyl peptidase IV inhibitor;

25 (b) an insulin sensitizer selected from the group consisting of a PPAR γ agonist, a PPAR α/γ dual agonist, a PPAR α agonist, a biguanide, and a protein tyrosine phosphatase-1B inhibitor;

(c) an insulin or insulin mimetic;

30 (d) a sulfonylurea or other insulin secretagogue;

(e) an α -glucosidase inhibitor;

(f) a glucagon receptor antagonist;

(g) GLP-1, a GLP-1 mimetic, or a GLP-1 receptor agonist;

(h) GIP, a GIP mimetic, or a GIP receptor agonist;

(i) PACAP, a PACAP mimetic, or a PACAP receptor agonist;

(j) a cholesterol lowering agent such as (i) HMG-CoA reductase inhibitor, (ii) sequestrant, (iii) nicotinyl alcohol, nicotinic acid or a salt thereof, (iv) PPAR α agonist, (v) PPAR α/γ dual agonist, (vi) inhibitor of cholesterol absorption, (vii) acyl CoA:cholesterol acyltransferase inhibitor, and (viii) anti-oxidant;

5 (k) a PPAR δ agonist;
 (l) an antiobesity compound;
 (m) an ileal bile acid transporter inhibitor;
 (n) an anti-inflammatory agent; and
 (o) an antihypertensive agent.

10

27. The pharmaceutical composition of Claim 26 wherein the PPAR α/γ dual agonist is KRP-297.

15 28. A method of treating diabetes in a mammal in need thereof comprising administering to the mammal a therapeutically effective amount of a compound of Claim 1 in combination with the PPAR α/γ dual agonist KRP-297.